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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/837,806	04/18/2001	Sudhir Agrawal	HYZ-069CN (47508-407)	8489

7590 01/13/2005

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/837,806	AGRAWAL, SUDHIR	
	Examin r	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on **10-20-04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-11,14-16,18-26 and 29-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-11,14-16,18-26 and 29-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-20-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 10-20-04.

Claims 1, 4-11, 14-16, 18-26, 29-39 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Maintained Rejections

Claims 14, 15, and 34-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting HIV-1 or HIV-2 infection in a cell in vitro comprising contacting the cell with an anti-gag specific antisense oligonucleotide, does not reasonably provide enablement for inhibiting HIV infection in a cell in vivo for the same reasons of record set forth in the previous Office action mailed 6-16-04.

Applicant's arguments filed 10-20-04 have been fully considered but they are not persuasive. Applicants argue that the claimed invention is fully enabled because it is neither overly broad in scope nor requires undue experimentation. The claims are drawn to compositions and methods for inhibiting HIV-1 or HIV-2 infection in cells in vitro or in vivo comprising the administration of antisense oligonucleotides comprising an oligonucleotide that is 21 nucleobases in length from SEQ ID NO: 5 (the latter whose length is 22 nuclebases) and optionally comprising at least two 3'-terminal and/or at least two 5'-terminal ribonucleotides that are substituted with 2'-O-alkyl ribonucleotides.

Applicants argue that this scope is enabled for in vivo inhibition of HIV-1 and HIV-2 infections because a larger oligonucleotide (*a.k.a.* GEM91) of 25 nucleobases - which comprises phosphorothioate internucleoside linkages and comprises within its nucleotide sequence these smaller, instantly claimed oligonucleotides - has successfully inhibited HIV-1 infection in humans as demonstrated in Exhibit C (filed 10-20-04) in human clinical trial data. Applicants argue further that, although this 25mer oligonucleotide was withdrawn from clinical trials because of its toxic effects, it nevertheless successfully inhibited viral infection in humans. In addition, Applicants argue that one of the instantly claimed oligonucleotides (GEM92, SEQ ID NO: 1, which is a phosphorothioated 21mer derived from the larger 25mer and which contains 2'-O-methyl groups at the 5' and 3' termini) has demonstrated effective oral delivery in humans and excellent safety results. Applicants additionally argue that the instantly claimed 21-mers have inhibited HIV-1 infection in target cells (e.g. MT-4 cells) in vitro.

Applicants are correct that the instantly claimed oligonucleotides are enabled for introducing intact oligonucleotides into a mammal and for exhibiting effective bioavailability, and are enabled for in vitro inhibition of viral infection using the shorter oligonucleotides claimed. Contrary to Applicants' assertions, however, the successful in vivo inhibition demonstrated by the larger antisense (GEM91) is not representative of the in vivo ability of the shorter antisense oligonucleotides for inhibiting viral infections. The success of the larger oligonucleotide is not predictive of the other, shorter oligonucleotides' ability to successfully target and inhibit viral infection in vivo. The larger, previously tested oligonucleotide has the additional nucleotides that possibly

confer efficacy upon the molecule's ability to inhibit expression of the gag gene in vivo. But the efficacy demonstrated using this particular antisense does not mean that a shorter antisense derived from the larger's sequence has the ability to do the same. (Please see Branch, who points out that the unpredictability of antisense "confounds research applications of nucleic acid reagents. ...The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules." (second and third full paragraphs on p. 45) It would therefore require undue experimentation to determine the ability of these shorter oligonucleotides to inhibit HIV infections in vivo. The reduced toxicity and successful bioavailability demonstrated by the shorter, 2'-O-substituted oligonucleotides are not representative of the ability to target and inhibit expression of HIV-1 or HIV-2 in vivo.

Likewise, the in vitro ability of these shorter oligonucleotides to inhibit HIV infection in appropriate target cells is not representative or correlative of the ability to do so in vivo. (Please see Crooke at first full paragraph on p. 3: [E]xtrapolations from in vitro uptake studies to predictions about in vivo pharmacokinetic behavior ar entirely inappropriate and, in fact, there are now several lines of evidence in animals and man to demonstrate that, even after careful consideration of all in vitro uptake data, one cannot predict in vivo phamacokinetics of the compounds based on in vitro studies.") The concentrations of oligonucleotides administered and successfully delivered to target cells in culture, and which provide for effective in vitro viral inhibition, do not necessarily reflect the concentrations required for achieving in vivo viral inhibition of these particular

antisense oligonucleotides. It is the lack of predictability in comparing the results of successfully using a longer antisense oligonucleotide to achieve in vivo inhibition with those of shorter antisense, and the lack of predictability in extrapolating in vitro results to in vivo efficacy regarding the shorter antisense claimed, that render the instant invention not enabled for the full scope claimed.

Claims 1, 4, 5, 8 and 9 are rejected under 35 U.S.C. 102(a) or (e) as anticipated by Agrawal et al for the same reasons of record set forth in the previous Office action mailed 6-16-04.

Applicant's arguments filed 10-20-04 have been fully considered but they are not persuasive. Applicants argue that the cited reference of Agrawal ((USPN 5,591,721) does not properly anticipate the claimed invention because the oligonucleotides in Table 1 of Agrawal are each 25 nucleotides in length, not 21 nucleotides in length as required by Applicant's claimed embodiments of the invention. Applicant is correct that Table of the Agrawal reference are at least 25 nucleotides in length or more. Furthermore, the sequences disclosed in this table comprise the sequences claimed. But, contrary to Applicant's assertions, the claimed invention is not limited to oligonucleotides consisting of 21 nucleotides as suggested by Applicant, but is drawn to "[a] synthetic oligonucleotide comprising a nucleotide sequence consisting 21 nucleotides of the sequence set forth as SEQ ID NO: 5" (see lines 1-2, claim 1). Since comprising language is used in the claim, these oligonucleotides can be larger than the 21mers

derived from SEQ ID NO:5. Therefore, the claimed invention is properly anticipated by Agrawal.

Claims 1, 4, 5-11, 14-16, 18-26, 29-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al in view of Hovanessian et al and Goodchild et al insofar as the claims are drawn to compositions and methods of inhibiting HIV-1 or HIV-2 infection in a cell in vitro comprising the administration of oligonucleotides 21 nucleobases in length specifically complementary to nucleotides 324-345 of HIV-1 gag of SEQ ID NO: 5, which oligonucleotides comprise SEQ ID Nos: 1 and 3, and which oligonucleotides are linked via phosphorothioate internucleotide linkages, and further comprise at least two 5' and/or 3'-terminal ribonucleotides comprising 2'-O-methyl moieties, for the same reasons of record set forth in the previous Office action mailed 6-16-04.

Applicant's arguments filed 10-20-04 have been fully considered but they are not persuasive. Applicants argue that the references of Hovanessian and Goodchild do not cure the deficiencies of Agrawal. Contrary to Applicants' assertions and as addressed in the paragraph above, Agrawal properly anticipates the invention of claims 1, 4, 5, 8 and 9 because the invention is drawn to oligonucleotides comprising oligonucleotides 21 nucleobases in length and so Hovanessian and Goodchild are not relied upon to cure deficiencies of the 102 rejection set forth above.

Applicants additionally argue that Agrawal does not indicate that the sequences disclosed (e.g. in Table 1 of USPN 5,591,721) are complementary to the conserved gag

region of HIV-1 and therefore one of skill in the art would not have been motivated to specifically use the oligonucleotides claimed in the instant application to target and inhibit the HIV gag gene. And, according to Applicant, since Agrawal did not specifically disclose the target of the disclosed oligonucleotide sequences to be gag of HIV, then the combination of references cited fail to provide proper motivation to render the instant invention obvious. Contrary to Applicant's assertions, the failure to disclose the target gene of the oligonucleotides disclosed by Agrawal do not detract from the motivation provided by the combined teachings of Agrawal, Hovanessian and Goodchild to render the instant invention obvious. The oligonucleotides disclosed by Agrawal are easily identified by a routine sequence search to specifically target the gag gene of HIV. The sequence of the HIV gag target gene was well known in the art at the time the sequences were disclosed by Agrawal. In addition, both Hovanessian and Goodchild teach the motivation to target the previously characterized genome sequences of HIV for viral inhibition (e.g. see col. 1, 6-7 of Hovanessian and col. 4-6, 10-13 and claims 4 and 5 of Goodman). Furthermore, antisense inhibition was a well known technique known in the art at the time the invention was made. So, contrary to Applicants' assertions, the teachings of Hovanessian and Goodchild regarding inhibition of HIV infections, and the disclosure of the antisense oligonucleotides with their modifications for enhancing stability by Agrawal, render the instant invention obvious to one of ordinary skill in the art.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JZ
1-5-05

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